



General

Guideline Title

Canadian Headache Society guideline for migraine prophylaxis.

Bibliographic Source(s)

Pringsheim T, Davenport W, Mackie G, Worthington I, Aube M, Christie SN, Gladstone J, Becker WJ, Canadian Headache Society Prophylactic Guidelines Development Group. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012 Mar;39(2 Suppl 2):S1-59. [PubMed](#)

Guideline Status

This is the current release of the guideline.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines](#) : A U.S. Food and Drug Administration (FDA) review has found that the growing combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.
- [March 22, 2016 – Opioid pain medicines](#) : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

Recommendations

Major Recommendations

Definitions for the level of evidence (High, Moderate, Low, and Very low) and grade of recommendation (Strong-high quality evidence, Strong-moderate quality evidence, Strong-low quality evidence, Weak-high quality evidence, Weak-moderate quality evidence, Weak-low quality evidence) are provided at the end of the "Major Recommendations" field.

General Principles of Migraine Prophylaxis

Migraine Prophylaxis: General Considerations

When Should Migraine Prophylaxis Be Considered? (Expert Consensus)

- i. Migraine prophylactic therapy should be considered in patients whose migraine attacks have a significant impact on their lives despite appropriate use of acute medications and trigger management/lifestyle modification strategies.
- ii. Migraine prophylactic therapy should be considered when the frequency of migraine attacks is such that reliance on acute medications alone puts patients at risk for medication overuse (rebound) headache. Medication overuse is defined as use of opioids, combination analgesics, or triptans on ten days a month or more, or use of simple analgesics (acetaminophen, acetylsalicylic acid [ASA], non-steroidal anti-inflammatory drugs [NSAIDs]) on 15 days a month or more.
- iii. Migraine prophylaxis should be considered for patients with greater than three moderate or severe headache days a month when acute medications are not reliably effective, and for patients with greater than eight headache days a month even when acute medications are optimally effective because of the risk of medication overuse headache.
- iv. Migraine prophylaxis may be considered in some patients with relatively infrequent attacks according to patient preference and physician judgement, for example in patients with hemiplegic migraine.
- v. Migraine prophylaxis may be particularly useful for patients with medical contraindications to acute migraine therapies.

When Should Migraine Prophylactic Therapy Be Stopped? (Expert Consensus)

- i. A prophylactic medication trial should consist of at least two months at the target or optimal dose (or at the maximum tolerated dose if the usual target dose is not tolerated) before a prophylactic drug is considered ineffective.
- ii. A prophylactic medication is usually considered effective if migraine attack frequency or the number of days with headache per month is reduced by 50% or more, although lesser reductions in migraine frequency may be worthwhile, particularly if the drug is well tolerated.
- iii. In addition to reduction in migraine attack frequency or in the number of days with headache per month, reductions in headache intensity and migraine-related disability need to be considered when judging the effectiveness of prophylactic therapy.
- iv. Patients on migraine prophylaxis require periodic reevaluation both to monitor potential side effects and to assess efficacy.
- v. Because of its utility in assessing the effectiveness of prophylactic therapy, patients should be strongly encouraged to keep a headache diary/calendar.
- vi. After 6 to 12 months of successful prophylactic therapy, consideration should be given to tapering and discontinuing the prophylactic medication in many patients, although others may benefit from a much longer duration of prophylactic therapy. If headache frequency increases as the prophylactic drug dosage is reduced, the dosage can be increased again or the drug restarted if it has been discontinued.

Choosing a Prophylactic Drug (Expert Consensus)

- i. When prophylactic drug therapy is started, the patient should also be evaluated for the presence of acute medication overuse, and cessation of medication overuse should be strongly encouraged to optimize the chances of success. Medication overuse is defined as use of opioids, combination analgesics, or triptans on ten days a month or more, or use of simple analgesics (acetaminophen, ASA, NSAIDs) on 15 days a month or more.

Medications for Migraine Prophylaxis

Specific Prophylactic Medications

Antiepileptics

Divalproex Sodium/Sodium Valproate

Weak recommendation, high quality evidence: While there is high quality evidence that divalproex sodium 500 to 1500 mg per day is effective for migraine prophylaxis, a weak recommendation was made based on the risk benefit profile of this medication for many patients. Divalproex sodium often promotes weight gain and may cause reversible tremor and hair loss. It is usually avoided in women with child bearing potential. When considered for this patient group, it should be given with folic acid, and caution should be exercised with careful consideration of birth control status due to the potential risk for teratogenicity.

Gabapentin

Strong recommendation, moderate quality evidence: The guideline authors recommend that clinicians offer gabapentin at a target dose of at least

1200 mg per day to eligible patients for migraine prophylaxis.

Topiramate

Strong recommendation, high quality evidence: The guideline authors recommend that clinicians offer topiramate to eligible patients for migraine prophylaxis. The guideline authors found high quality evidence that topiramate provides a reduction in migraine frequency, though side effects from treatment are common. Due to the high number of adverse events and withdrawals on the 200 mg dose of topiramate, and the high quality evidence for a therapeutic benefit on the 100 mg dose, the recommended target dosage of topiramate for migraine prophylaxis is 100 mg per day. As was done in the clinical trials, the dosage should be increased gradually (see "Treatment Strategies: Pharmacological Prophylaxis," below).

Antidepressants

Amitriptyline

Strong recommendation, high quality evidence: The guideline authors recommend that clinicians offer amitriptyline 10 to 100 mg per day to eligible patients for migraine prophylaxis, although an occasional patient may require and tolerate higher doses.

Venlafaxine

Weak recommendation, low quality evidence: The guideline authors recommend that clinicians offer venlafaxine extended release at a target dose of 150 mg per day to eligible patients for migraine prophylaxes.

Antihypertensives and Other Calcium Channel Blockers

Propranolol

Strong recommendation, high quality evidence: The guideline authors recommend that clinicians offer propranolol at a target dose of 80 to 160 mg per day to eligible patients for migraine prophylaxis. Studies comparing propranolol to calcium channel blockers (mainly flunarizine), and metoprolol suggest comparative efficacy between treatments.

Metoprolol

Strong recommendation, high quality evidence: The guideline authors recommend that clinicians offer metoprolol (100 to 200 mg daily) to eligible patients for migraine prophylaxis.

Nadolol

Strong recommendation, moderate quality evidence: The guideline authors recommend that clinicians offer nadolol at a target dose of 80 to 160 mg per day to eligible patients for migraine prophylaxis.

Flunarizine

Weak recommendation, high quality evidence: While there is high quality evidence that flunarizine 10 mg per day is effective for migraine prophylaxis, a weak recommendation was made because treatment is often limited by side effects, including depression and weight gain.

Verapamil

Weak recommendation, low quality evidence: Although verapamil has long been used for migraine prophylaxis and generally has few side effects, the evidence that it is effective is very limited.

Lisinopril

Weak recommendation, low quality evidence: Although lisinopril 20 mg daily is generally well tolerated, the evidence for effectiveness is limited and the magnitude of benefit in migraine prophylaxis appears small.

Candesartan

Strong recommendation, moderate quality evidence: The guideline authors recommend that clinicians offer candesartan 16 mg per day to eligible patients for migraine prophylaxis. Although the evidence that candesartan provides a reduction in migraine frequency is limited, one good randomized trial supports its use and side effects of treatment are minimal.

Vitamins/Minerals/Herbals

Riboflavin

Strong recommendation, low quality evidence: The guideline authors recommend that clinicians offer riboflavin 400 mg per day to eligible patients for migraine prophylaxis. There is some evidence for benefit and side-effects are minimal.

Coenzyme Q10

Strong recommendation, low quality evidence: The guideline authors recommend that clinicians offer coenzyme Q10 300 mg per day (dosed as 100 mg three times daily) to eligible patients for migraine prophylaxis.

Magnesium

Strong recommendation, low quality evidence: The guideline authors recommend that clinicians offer magnesium to eligible patients for migraine prophylaxis. There is some evidence for benefit and side effects are minimal. Due to the contrary evidence presented in these trials, the guideline authors recommend that 24 mmol (600 mg) of elemental magnesium daily as magnesium citrate be used for migraine prophylaxis, since a positive result was only obtained with this compound.

Butterbur (*Petasites hybridus* Root Extract)

Strong recommendation, moderate quality evidence: The guideline authors recommend that clinicians offer butterbur 75 mg twice daily to eligible patients for migraine prophylaxis. The magnitude of benefit may be small, but side effects are minimal. Due to the contrary evidence presented in these two trials for the 50 mg dose, the guideline authors recommend that 75 mg of butterbur twice daily be used for migraine prophylaxis.

Caution: Only commercially prepared products in which plant carcinogens and hepatotoxic alkaloids have been removed and which have been standardized to contain a minimum of 15% petasins are recommended. Patients should be cautioned against consuming the plant in any other form.

Feverfew

Strong recommendation, moderate quality evidence: The guideline authors recommend against offering feverfew for the prophylaxis of migraine. The evidence indicates that feverfew is no better than placebo for the prophylaxis of migraine.

Botulinum Toxin Type A

Strong recommendation, high quality evidence: The guideline authors recommend against providing botulinum toxin type A for the prophylaxis of episodic migraine in patients with less than 15 headache days per month. The evidence indicates that botulinum toxin type A is no better than placebo for the prophylaxis of migraine in such patients.

Serotonin Antagonists

Pizotifen (Pizotyline)

Weak recommendation, high quality evidence: While there is high quality evidence that pizotifen 1.5 to 4 mg per day is effective for migraine prophylaxis, a weak recommendation was made based on the side effects commonly associated with this medication. Weight gain and sedation are common with pizotifen.

Drugs Not Included in the Systematic Review

Selective Serotonin Reuptake Inhibitors (Expert Consensus)

- i. Selective serotonin reuptake inhibitors are not recommended for the prophylaxis of migraine.

Other Tricyclic Antidepressants (Expert Consensus)

- i. Imipramine, trinitramine, desipramine, clonipramine, and doxepin are not recommended for routine use for migraine prophylaxis. Nortriptyline may be useful (expert opinion only).

Clonidine (Expert Consensus)

- i. Clonidine is not recommended for migraine prophylaxis.

Methysergide (Expert Consensus)

- i. Methysergide is an effective migraine prophylactic, but because of side-effects should only be used under specialist supervision.

Treatment Strategies: Pharmacological Prophylaxis

Migraine Prophylactic Treatment Strategies

First Time Strategies

Beta-Blocker Strategy (Expert Consensus)

- i. Propranolol, nadolol, and metoprolol are good initial prophylactic drug choices for many patients with migraine.
- ii. For propranolol the usual starting dose is 20 to 40 mg twice daily. The dose can be increased slowly (every one to two weeks) as necessary and tolerated up to a maximum of 160 mg daily. The long acting form may also be used.
- iii. For nadolol, the usual starting dose is 20 to 40 mg given once daily in the morning. The dose can be increased slowly (every one to two weeks) as necessary and tolerated, up to a maximum of 160 mg daily.
- iv. For metoprolol, the usual starting dose is 50 mg twice a day. The dose can be increased slowly (every one to two weeks) as necessary and tolerated to a maximum dose of 200 mg daily. The long acting form may also be used.

Tricyclic Strategy (Expert Consensus)

- i. Amitriptyline is a good initial migraine prophylactic drug. It may be particularly useful in patients with insomnia or associated tension-type headache.
- ii. When starting amitriptyline prophylaxis for migraine, a low initial dose should be used in most patients (10 mg) and the dose should be built up slowly (10 mg every week or every two weeks).
- iii. In patients without insomnia or in those who cannot tolerate amitriptyline, nortriptyline in similar doses may be better tolerated and possibly effective.

Low Side Effect Strategies

Low Side Effect Drug Strategy (Expert Consensus)

- i. Candesartan and lisinopril have evidence for efficacy in migraine prophylaxis, and generally have few side effects, although each has only one controlled trial to date supporting its use. The target dose for candesartan is 16 mg daily, for lisinopril 20 mg daily. Candesartan is preferred because of fewer side effects, and because clinical experience with lisinopril is more limited. Given the limited data for efficacy and the limited clinical experience with both these drugs at this time, they should not be considered as substitutes for the more established drugs in the "First time strategy" under most circumstances.

Low Side Effect Herbal/Vitamin/Mineral Strategy (Expert Consensus)

- i. Butterbur, riboflavin, magnesium, and co-enzyme Q have very few side effects, and are evidence based options for migraine prophylaxis. These compounds are felt to have only modest efficacy, and should not be considered substitutes for "First time" strategy drugs under most circumstances.

Increased Body Mass Index Strategy (Expert Consensus)

- i. Topiramate is a migraine prophylactic drug which, because of its propensity to promote weight loss, is particularly useful in patients who are overweight, in patients who are particularly concerned about weight gain, and in patients with co-existent illnesses which might be exacerbated by weight gain (i.e., diabetes).
- ii. Topiramate should be started at a low dose (15 or 25 mg daily), and the daily dose should be increased slowly (by 15 every week or 25 mg every two weeks in order to improve drug tolerability).
- iii. The usual target dose for topiramate in migraine prophylaxis is 100 mg daily.

Hypertension Strategy (Expert Consensus)

- i. For patients with hypertension and migraine, refer to the Canadian Hypertension Education Program (CHEP) clinical practice recommendations which are updated annually and can be found at www.hypertension.ca [redacted]. The following recommendations for managing patients with both migraine and hypertension have been reviewed with CHEP and are consistent with those evidence based recommendations. The specific angiotensin receptor blockers and angiotensin converting enzyme inhibitors listed below are those with evidence for efficacy in migraine prophylaxis.
- ii. Simplification of medical regimens is known to improve adherence, and the use of the same medication for both migraine and hypertension may reduce the potential for drug side effects and interactions. Recommended options are:

- a. Propranolol, nadolol, or metoprolol (for patients under age 60). (Some other beta-blockers may also be effective, but have not been reviewed in this guideline.)
- b. Candesartan (Candesartan has also demonstrated efficacy for patients with isolated systolic hypertension.)
- c. Lisinopril (Angiotensin-converting-enzyme [ACE] inhibitors have been found to be less effective for lowering blood pressure as monotherapy in patients of African [black] origin.)
- iii. Combination therapy is often required to achieve blood pressure targets. For patients requiring additional medication for blood pressure control, adding a thiazide diuretic and/or a calcium channel blocker to one of the above medications is indicated (combinations of beta blockers and nondihydropyridine calcium channel blockers like verapamil should be avoided due to the risk of heart block).
- iv. If adequate migraine prophylaxis is not achieved and the blood pressure is at target, other migraine prophylactic medications may be added.

Depression/Anxiety Strategy (Expert Consensus)

- i. Because of the advantages of monotherapy (less potential for drug interactions and side effects), monotherapy with one of amitriptyline or venlafaxine should be considered in patients with anxiety and/or depression who require migraine prophylaxis. Experience with venlafaxine in migraine prophylaxis is limited. Nortriptyline may be an alternative although less evidence-based choice.
- ii. In some patients, particularly if good control is not achieved with monotherapy or if the patient is unable to tolerate adequate doses of the tricyclic, clinicians may need to treat the migraine and the anxiety and/or depression with separate medications.
- iii. If selective serotonin re-uptake inhibitors [SSRI]–tricyclic co-therapy is planned, sertraline should be considered because of less potential for drug interactions. Most other SSRIs, in particular fluoxetine, fluvoxamine, and paroxetine, have a greater potential for significant drug interactions with amitriptyline and nortriptyline.
- iv. Certain migraine prophylactic drugs should typically be avoided (flunarizine), or used with caution (topiramate) in patients with depression. Although traditionally beta-blockers have been considered to predispose to depression, more recent studies suggest that this is not the case.

Additional Monotherapy Drug Strategies (Expert Consensus)

- i. Topiramate is a useful migraine prophylactic drug. Although used for first time prophylaxis by some clinicians, it is not included here in the "First time" strategies because of its side effect profile. An exception is when it is used as part of the increased body mass index strategy.
- ii. Divalproex sodium is a useful migraine prophylactic drug in patients when other prophylactic drugs have failed. Given its teratogenicity, it should generally be avoided in women with child bearing potential and if used, should only be used when the benefits are felt to outweigh the risks, and with appropriate contraception in place.
- iii. Gabapentin can be considered in patients when other prophylactics have failed. It has the advantage of few drug interactions. Evidence for efficacy is less strong than for some other prophylactics.
- iv. Flunarizine can be a useful prophylactic when other prophylactics have failed, but should be avoided in patients with a significant history of depression. Patients on flunarizine should be monitored for onset of depression.
- v. Pizotifen is an option for migraine prophylaxis when other drugs have failed.
- vi. Verapamil can be considered for migraine prophylaxis when other drugs have failed, but the quality of evidence for efficacy of verapamil is low.
- vii. Although onabotulinumtoxinA is useful in chronic migraine, on the basis of clinical trial results it is not recommended for patients with episodic migraine (14 headache days per month or less).
- viii. Based on their proven efficacy in episodic migraine, many of the prophylactic drugs listed in this guideline are also utilized in chronic migraine. However, with the exception of topiramate and onabotulinumtoxinA, the evidence for most migraine prophylactic drugs for efficacy in chronic migraine is very limited.

Refractory Patient Strategy (Expert Consensus)

- i. The simultaneous use of more than one prophylactic drug may be of benefit in patients with migraine refractory to prophylactic monotherapy.
- ii. The following drug combinations may be useful in patients with refractory migraine, based primarily on non-randomized trials and clinical experience: beta-blockers and topiramate, beta-blockers and divalproex sodium, beta-blockers and amitriptyline, and amitriptyline and topiramate.
- iii. Patients requiring prophylactic polypharmacy should be considered for specialist referral.

Migraine during Pregnancy Strategy (Expert Consensus)

- i. Migraine drug prophylaxis is best avoided during pregnancy if at all possible. Strategies involving trigger management, maintenance of good hydration, regular meals, regular sleep, and attention to other lifestyle factors should be considered.
- ii. Magnesium is considered the safest migraine prophylactic during pregnancy.

- iii. If migraine drug prophylaxis is necessary during pregnancy, the best choice is a beta-blocker (propranolol or metoprolol) or if these are contraindicated or ineffective, amitriptyline or nortriptyline.

Migraine during Lactation Strategy (Expert Consensus)

- i. Migraine prophylaxis should be avoided during breast feeding, if possible.
- ii. Magnesium and the beta-blockers (propranolol, metoprolol, and nadolol) are the preferred choices if migraine prophylaxis is necessary during lactation.
- iii. Amitriptyline and nortriptyline may be considered for prophylaxis during lactation if magnesium and beta-blockers are contraindicated or ineffective.
- iv. Although divalproex sodium is considered compatible with breastfeeding, it may be best avoided due to the possibility of pregnancy in this population.

Table. Summary of Recommendations*

Recommended For Use in Episodic Migraine** (Use)		
	Recommendation	
Drug	Recommendation Strength	Quality of Evidence
Topiramate	Strong	High
Propranolol	Strong	High
Metoprolol	Strong	High
Amitriptyline	Strong	High
Nadolol	Strong	Moderate
Gabapentin	Strong	Moderate
Candesartan	Strong	Moderate
Butterbur	Strong	Moderate
Riboflavin	Strong	Low
Coenzyme Q10	Strong	Low
Magnesium citrate	Strong	Low
Divalproex	Weak	High
Flunarizine	Weak	High
Pizotifen	Weak	High
Venlafaxine	Weak	Low
Verapamil	Weak	Low
Lisinopril	Weak	Low
Not Recommended for Use in Episodic Migraine** (Do not use)		
Botulinum toxin type A	Strong	High
Feverfew	Strong	Moderate

*Utilizing Grading of Recommendations Assessment, Development and Evaluation (GRADE) Criteria; **Migraine with headache on less than 15 days a month.

Definitions:

Levels of Evidence: GRADE System

Level of Evidence	Definition
High	The guideline authors are confident that the true effect lies close to the estimate given by the evidence available.
Moderate	The guideline authors are moderately confident in the effect estimate, but there is a possibility it is substantially different.

Level of Evidence	Definition
Low	The confidence in the effect estimate is limited. The true effect may be substantially different.
Very Low	The guideline authors have little confidence in the effect estimate.

Recommendation Grades: Meaning and Clinical Implications*

Recommendation Grade	Benefits versus Risks	Clinical Implication
Strong – high quality evidence	Benefits clearly outweigh risks and burdens for most patients	Can apply to most patients in most circumstances
Strong – moderate quality evidence	Benefits clearly outweigh risks and burdens for most patients	Can apply to most patients, but there is a chance the recommendation may change with more research
Strong – low quality evidence	Benefits clearly outweigh risks and burdens for most patients	Can apply to most patients, but there is a good chance the recommendation could change with more research
Weak – high quality evidence	Benefits are more closely balanced with risks and burdens for many patients	Whether a medication is used will depend upon patient circumstances
Weak – moderate quality evidence	Benefits are more closely balanced with risks and burdens for many patients	Whether a medication is used will depend upon patient circumstances, but there is less certainty about when it should be used
Weak – low quality evidence	Benefits are more closely balanced with risks and burdens	There is considerable uncertainty about when to use this medication

*Only categories used in the guideline are shown.

Clinical Algorithm(s)

Appendix III of the original guideline document includes an algorithm which summarizes the migraine prophylactic treatment strategies.

Scope

Disease/Condition(s)

Episodic migraine (headache on ≤ 14 days a month)

Note: Though it is likely that physicians may extrapolate from the evidence presented here and use it for the care of patients with higher migraine frequencies, the literature reviewed for these guidelines did not include patients with chronic migraine (headache on >14 days a month).

Guideline Category

Management

Prevention

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Patients

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To assist the physician in choosing an appropriate prophylactic medication for an individual with migraine, based on current evidence in the medical literature
- To assist the practitioner in:
 - Determining which patients need prophylaxis
 - How long prophylaxis should be continued

Target Population

Patients with episodic migraine (headache on ≤ 14 days a month) who:

- Suffer a significant degree of disability as a result of their migraine, and for whom acute medication treatment has not proved sufficient to minimize this disability
- May be responding well to their symptomatic medications, but in whom a high frequency of acute medication use may place them at risk for medication overuse headache or significant systemic side effects

Interventions and Practices Considered

1. Consideration of migraine prophylaxis for patients whose migraine attacks have a significant impact on their lives and are at risk for medication overuse
2. Evaluation for medication overuse before prophylactic therapy
3. Tapering and discontinuation of successful therapy after 6 to 12 months
4. Prophylactic medication trial
5. Daily headache diary
6. Periodic reevaluation to monitor side effects and assess efficacy
7. Prophylactic strategies based on patient clinical features:
 - For first time (e.g., beta-blocker and tricyclic)
 - For low side effects
 - For increased body mass index
 - For hypertension
 - For depression/anxiety
 - For refractory patient
 - For migraine during pregnancy or lactation

Major Outcomes Considered

- Headache frequency (the number of migraine attacks or migraine days per month)

- Responder rate (proportion of patients achieving a 50% decrease in the frequency of migraine attacks in comparison to baseline)
- Prevalence of adverse events

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The recommendations for individual prophylactic drugs in the Guideline are based on a systematic review. For other aspects of the guideline document which deal with more general questions pertinent to migraine prophylaxis where randomized trials do not exist, a general literature review was done.

Systematic Review

Search Methods for Identification of Studies

For the identification of studies included or considered for this guideline, a detailed search strategy was developed for Ovid MEDLINE (1950 to April 2008) and EMBASE (1980 to April 2008). The search strategy combined the subject search with a highly sensitive search strategy for randomized controlled trials. The subject search used a combination of controlled vocabulary and free-text terms. Search terms used were: i) migraine disorders/pc or migraine with aura/pc or migraine without aura/pc (1,283); ii) limit 1 to (humans and [controlled clinical trial or meta analysis or randomized controlled trial]) (282). More details on the literature search are given in Appendix 2, Section 8 of the original guideline document. A review article based on this systematic review has been published previously. A second literature search was carried out in June 2011, using the same search terms, in order to update the literature review.

In addition, the Cochrane Collaboration Library was searched for systematic reviews of agents used for migraine prophylaxis. Cochrane systematic reviews were used to summarize trial data if similar inclusion criteria and methodology were used in the review.

Criteria Used for Including/Excluding Evidence Identified by the Search

- Studies were required to be prospective, randomized, double blind, controlled trials of drugs used to prevent the occurrence of migraine attacks.
- Trials comparing treatments to placebo or an active comparator were included.
- Both parallel group and cross-over designs were acceptable.
- Study participants had to be adults and meet International Headache Society (IHS) or Ad Hoc Committee on Classification of Headache (Ad Hoc) criteria for the diagnosis of migraine headache, or provide sufficient detail of the headache characteristics to support the diagnosis of migraine (for studies conducted prior to development of Ad Hoc criteria).
- The literature search was limited to agents commonly used in clinical practice, as explained in the text.
- Trials of patients with chronic daily headache (headache on ≥ 15 days per month), chronic tension type headache or transformed migraine were not included.

Number of Source Documents

Initial search: 59 studies and one Cochrane systematic review

Updated literature search: Eight additional publications reporting relevant clinical trials and two additional published meta-analyses

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence: Grading of Recommendations Assessment, Development and Evaluation (GRADE) System

Level of Evidence	Definition
High	The guideline authors are confident that the true effect lies close to the estimate given by the evidence available.
Moderate	The guideline authors are moderately confident in the effect estimate, but there is a possibility it is substantially different.
Low	The confidence in the effect estimate is limited. The true effect may be substantially different.
Very Low	The guideline authors have little confidence in the effect estimate.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The recommendations for individual prophylactic drugs in the guideline are based on a systematic review. For other aspects of the guideline document which deal with more general questions pertinent to migraine prophylaxis where randomized trials do not exist, a general literature review was done and expert opinion was used to draw conclusions regarding suggested management. These conclusions are clearly labelled as "Expert consensus" rather than recommendations in order to avoid confusion.

Systematic Review

Methods of the Review

Titles and abstracts of studies identified by the literature search were screened for eligibility by two independent reviewers. Papers that could not be excluded with certainty on the basis of the information contained in the title or abstract were retrieved in full for screening. Papers passing the initial screening process were retrieved and the full text was reviewed independently by two reviewers. For the literature update search done in June 2011, full text articles were again reviewed independently by two reviewers.

Assessment of Individual Clinical Trials

Studies were graded with respect to methodological quality using criteria developed by the US Preventive Services Task Force. Studies are rated "good" if all of the following criteria are met: assembly of comparable groups, adequate randomization, allocation concealment, confounders distributed equally, maintenance of comparable groups, absence of overall high or important differential loss to follow-up, measurement instruments are acceptable and applied equally, masking of outcome assessment, clear definition of interventions, all important outcomes considered and intention to treat analysis performed. A "fair" study does not meet all criteria but has no fatal flaw that invalidates its results. A "poor" study contains a fatal flaw. Fatal flaws include the assembly of non-comparable groups, the use of unacceptable or unequally applied measurements, lack of blinding of outcome assessment, failure to address key confounders, and lack of intention to treat analysis.

Statistical Methods

Meta-analysis was performed by treatment type where appropriate if more than one trial was identified. Odds ratios (ORs) were calculated for the responder rate (proportion of study subjects with a decrease in their migraine attack frequency of at least 50%) relative to placebo. ORs from multiple studies were tested for homogeneity using the chi-squared test and by calculating the I^2 statistic. If study estimates were homogenous, they were combined using a fixed-effects model. When studies with heterogeneous results were clinically similar, the study estimates were combined using a random-effects model. Clinical heterogeneity was assessed by looking at trial and patient characteristics, and outcome measures. Clinically heterogeneous studies were not statistically combined.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The main clinical question which this guideline aims to help answer for the medical practitioner is, "Which prophylactic drug should be prescribed for an individual patient in a specific clinical situation."

The recommendations for individual prophylactic drugs in the Guideline are based on a systematic review. For other aspects of the guideline document which deal with more general questions pertinent to migraine prophylaxis where randomized trials do not exist, a general literature review was done and expert opinion was used to draw conclusions regarding suggested management. These conclusions are clearly labelled as "Expert consensus" rather than recommendations in order to avoid confusion.

Professional Groups Involved in the Creation of These Guidelines

These guidelines were produced by the Canadian Headache Society. Health professionals involved in development of the guideline included neurologists, family physicians, nurses and pharmacists with a special interest in headache.

Patient Views and Preferences

Patient expectations, views, and preferences were obtained from the medical literature. Several publications dealing specifically with patient acceptance of migraine prophylactic therapy are referenced and discussed in the prophylactic treatment strategies section.

Patient views and experiences were also obtained at the Canadian Migraine Forum which was hosted by the Canadian Headache Society prior to the development of these guidelines.

Methods Used to Formulate the Recommendations

Papers were reviewed independently by two reviewers and graded with regard to methodological quality. The literature review, and draft recommendations were presented to five headache experts from the Canadian Headache Society Executive and membership on June 20, 2008, and consensus reached through discussion and mutual agreement.

The guidelines and the recommendations were refined through email correspondence and discussion with nine neurologists and two family physician members of the Canadian Headache Society, a nurse with extensive experience in the care of patients with headache, and a pharmacist. The guidelines were further discussed and validated with a group of Canadian headache experts on June 8, 2010, and with a second larger group on October 1, 2010 where the expert consensus statements were specifically discussed. Consensus was reached through discussion. Finally, the recommendations were graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system with a third consensus group consisting of eight neurologists, one nurse and one pharmacist on June 16, 2011.

Rating Scheme for the Strength of the Recommendations

Recommendation Grades: Meaning and Clinical Implications*

Recommendation Grade	Benefits versus Risks	Clinical Implication
Strong – high quality evidence	Benefits clearly outweigh risks and burdens for most patients	Can apply to most patients in most circumstances
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Weak – high quality evidence	Benefits are more closely balanced with risks and burdens for many patients	Whether a medication is used will depend upon patient circumstances
Weak – moderate quality evidence	Benefits are more closely balanced with risks and burdens for many patients	Whether a medication is used will depend upon patient circumstances, but there is less certainty about when it should be used

Recommendation Evidence	Benefits versus Risks Benefits are more likely balanced with risks and burdens	Clinical Implication uncertainty about when to use this medication

*Only categories used in the guideline are shown.

Cost Analysis

If prophylactic medications are prescribed more frequently than in the past for patients with migraine as a result of these guidelines, this has the potential to increase demand on physician offices and to increase prophylactic drug costs. On the other hand, several studies have shown that migraine drug prophylaxis reduces the cost of symptomatic medications significantly, so that the overall drug costs may be unchanged, reduced, or affected less than might be expected.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

External Review of the Guideline

The guidelines were externally reviewed by three experts not involved in the Guideline Development Group. Reviewers were asked to critically review the guidelines, and their feedback was considered by the Guideline Development Group. These reviewers included:

- A neurologist
- A family physician
- A pharmacist

Internal Review

Other members of the Canadian Headache Society Prophylactic Guidelines Development Group participated in consensus groups and/or provided feedback on manuscript drafts.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is specifically stated for most recommendations in the "Medications for Migraine Prophylaxis" section (see the "Major Recommendations" field). For other recommendations, expert opinion was used to draw conclusions.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate choice and management of prophylactic medications for individuals with migraine for a potential reduction in headache frequency, headache intensity and migraine-related disability
- These guidelines might reduce the burden of patient follow up if physicians are more likely to choose the best drug for the patient first as a result of these guidelines.

Potential Harms

- Most medications used for migraine prophylaxis have potential side effects, and the risk-benefit ratio for an individual patient needs to be considered whenever prophylaxis is initiated. See Table 2, Section III of the original guideline document for a list of all the recommended drugs and adverse effects.
- Only commercially prepared products of butterbur in which plant carcinogens and hepatotoxic alkaloids have been removed and which have been standardized to contain a minimum of 15% petasins are recommended. Patients should be cautioned against consuming the plant in any other form.
- Other guidelines have concluded *methysergide* could only be recommended for short term use (maximum six months) because of potentially serious side effects (retroperitoneal fibrosis and other fibrotic syndromes).
- Possible disadvantages of treating the migraine and the anxiety and/or depression with separate medications are more drug side effects, and the potential for drug interactions.

Contraindications

Contraindications

- Some prophylactic medications may be contraindicated by certain co-existent medical conditions (for example flunarizine in depression, or a beta-blocker in asthma).
- Divalproex sodium is usually avoided in women with child bearing potential. When considered for this patient group, it should be given with folic acid, and caution should be exercised with careful consideration of birth control status due to the potential risk for teratogenicity.
- A recent health care professional letter from the manufacturer of topiramate stated that for the indication of migraine prophylaxis, topiramate is contraindicated in pregnancy and in women of childbearing potential who are not using an effective method of contraception.

Qualifying Statements

Qualifying Statements

- This guideline is designed to offer evidence-based strategies for the prophylactic treatment of migraine. It is not, however, intended to replace clinical judgment or establish a treatment protocol for all individuals with migraine. Although every attempt has been made to provide current information, it is the responsibility of the practitioner to ensure that drugs and dosages are used correctly.
- It should also be noted that although the treatment strategies presented in Section III of the original guideline document are broadly based on evidence from clinical trials, they also include a significant component of clinical judgment and expert opinion. Therefore, some of the recommendations in this strategy section may be controversial.
- It should be noted that migraine prophylaxis is an "off label" use for most of the medications listed in these migraine strategies. To date, only three of these drugs, flunarizine, topiramate, and pizotifen have received an official Health Canada indication for migraine prophylaxis.

Implementation of the Guideline

Description of Implementation Strategy

Options for Measuring Guideline Adherence

- a. The decision to start migraine pharmacological prophylaxis must be individualized and many factors need to be taken into consideration. If a practice audit is planned, all patients with more than five migraine days a month could be reviewed as to whether prophylaxis was considered and/or prescribed. However, it should be recognized that some of these patients would have decided against prophylaxis for a variety of reasons. The appropriateness of prophylactic initiation in a practice could be assessed, based on the two prime indications for prophylaxis: the presence of significant disability despite optimal symptomatic treatment or use of symptomatic medications at a frequency which puts the patient at risk for medication overuse headache.

- b. With regard to appropriateness of prophylactic drug choice in a practice, this could be evaluated by determining whether drugs with a strong recommendation for use were used primarily (see Table: "Summary of Recommendations" in the "Major Recommendations" field), and whether an appropriate treatment strategy was chosen for an individual patient, based on the clinical setting (see Table: "Prophylactic Drug Treatment Strategies, Based on the Clinical Setting" in the original guideline document).

Tools Have Been Made Available to Assist in Dissemination and Implementation

- a. A summary document for family physicians has been included (Section 4 of the original guideline document).
- b. An algorithm which summarizes the prophylactic treatment strategies has been included (Appendix 3 of the original guideline document).
- c. A guideline summary for patients and the public has been included (Section 5 of the original guideline document).
- d. A patient leaflet which describes migraine preventive treatment has been included (Appendix 3 of the original guideline document).
- e. A patient headache diary sheet together with instructions for completion (Appendix 3 of the original guideline document)

Implementation Tools

Chart Documentation/Checklists/Forms

Clinical Algorithm

Patient Resources

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

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Guideline Developer(s)

Canadian Headache Society - Professional Association

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Canadian Headache Society Prophylactic Guidelines Development Group

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Conflicts of Interest: *Pringsheim, T* - Dr. Pringsheim has received an educational grant from Teva Neuroscience. *Becker, WJ* - Dr. Becker has served on Advisory Boards and/or done clinical trials for and/or received speaker's honoraria from: Allergan, Merck, AGA Medical, Medtronic, Teva, Johnson and Johnson, and Pfizer. *Worthington, I* - Ms. Worthington has served on Advisory Boards and/or received honoraria (speaker, consultation, and travel to headache conferences) from: Merck Frosst, GlaxoSmithKline, and AstraZeneca. *Aubé, M* - Dr. Aubé has served on Advisory Boards and/or done clinical trials for and/or received speaker's honoraria from Merck, Teva, Johnson and Johnson, and Pfizer. *Christie, SN* - Dr. Christie has served on Advisory Boards and/or received Research Grants, Speaker Honoraria/Educational Grants from Merck Frosst, Allergan, Pfizer, Teva, and Johnson and Johnson. *Gladstone, JP* - Dr. Gladstone has served on Advisory Boards and/or been involved with clinical trials for and/or received educational grants/speaker's honoraria from: Allergan, Merck, Teva, Johnson & Johnson, and Pfizer. He holds investments in Allergan. *Gawel, M* - Dr. Gawel has served on Advisory Boards and/or received research funding from GlaxoSmithKline, Pfizer Allergan, Merck, Janssen, Neuraxon, Allergan, AstraZeneca, and Abbott. *Leroux, E* - Dr. Leroux has served on Advisory Boards for and/or received honoraria from Allergan, Merck, Pfizer, and Johnson and Johnson. Her institution (Hôpital Notre-Dame, Montreal, QC, Canada) has received grants from Pfizer, Merck, and Teva Neuroscience. *Robinson, G* - Dr. Robinson has served on Advisory Boards and/or received speaker's honoraria from Allergan, Merck, Teva, Johnson and Johnson, and Pfizer. *Richer, L* - Dr. Richer has served on Advisory Boards and/or participated in clinical trials with Janssen-Ortho, Allergan, and Merck. *Giammarco R* - Dr. Giammarco has served on Advisory Boards for or

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Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the [Headache Network Canada Web site](#) .

Availability of Companion Documents

A summary for primary care physicians is available in Section IV of the [original guideline document](#) .

Patient Resources

A summary for patients and their families is available in Section V and a patient information leaflet is available in Appendix III of the [original guideline document](#) .

A sample headache clinic diary, sample diary, and headache pain scale are available from the [Headache Network Canada Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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